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PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Case No. 02-090-B

In re Application of:

Bakthavatchalam *et al.*

Serial No.: 09/910,442

Filed: July 20, 2001

For: Capsaicin Receptor Ligands

Before the Examiner:
Kahsay Habte

Art Unit: 1624

**RESPONSE TO THE OFFICE ACTION**
**MAILED MARCH 4, 2003**

Commissioner for Patents
Alexandria, VA 22313

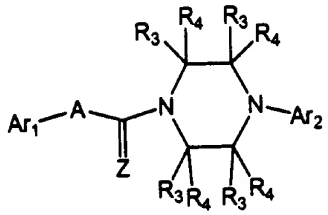
Dear Sir:

Responsive to the Office Action mailed March 4, 2003, Applicants respectfully request the Examiner to reconsider the above-identified patent application in view of the following Amendments and Remarks.

## AMENDMENTS

1-3. (Cancelled)

4. (Currently Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, $NR_A$, $NR_ACR_BR_B'$, $CR_B\ R_B'NR_A$, $-CR_A=CR_B-$, and $C_3H_4$; where $R_A$, $R_B$, and $R_B'$ are independently selected at each occurrence from hydrogen and alkyl;

Z is oxygen or sulfur;

each $R_3$ and $R_4$ is independently

(a) selected from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; -COOH; -CHO; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted



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alkylthio; optionally substituted alkyl ketone; optionally substituted alkylester; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted mono- or di-alkylcarboxamide; optionally substituted -$S(O)_nNH$alkyl; optionally substituted -$S(O)_nN$(alkyl)(alkyl); optionally substituted -NHC(=O)alkyl; optionally substituted -NC(=O)(alkyl)(alkyl); optionally substituted -$NHS(O)_n$alkyl; optionally substituted -$NS(O)_n$(alkyl)(alkyl); optionally substituted saturated heterocyclic ring or partially unsaturated heterocycle of from 5 to 8 atoms, which saturated heterocyclic ring or partially unsaturated heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; and optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring independently selected from the group consisting of N, O, and S; or

(b) joined to a $R_3$ or $R_4$ not attached to the same carbon to form an optionally substituted aryl ring, a



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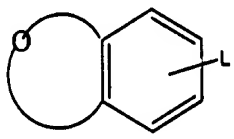
saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is optionally substituted, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally substituted and contains 1, 2, or 3 heteroatoms selected from N, O, and S;

$Ar_1$ is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with $R_5$; and

(b) bicyclic oxygen-containing groups of the formula:



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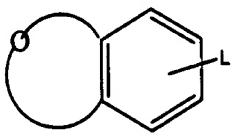
optionally mono-, di-, or trisubstituted with $R_5$, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

$Ar_2$ is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, [pyrazinyl,] benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with $R_5$; and

(b) bicyclic oxygen-containing groups of the formula:




optionally mono-, di-, or trisubstituted with $R_5$, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing



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ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

$R_5$ is independently selected at each occurrence from the group consisting of halogen, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$, $C_{2-6}$alkynyl substituted with 0-2 $R_6$, $C_{1-6}$alkoxy and Y;

$R_6$ is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $-S(O)_n(C_{1-4}alkyl)$, halo($C_{1-4}$)alkyl, halo($C_{1-4}$)alkoxy, $CO(C_{1-4}alkyl)$, $CONH(C_{1-4}alkyl)$, $CON(C_{1-4}alkyl_1)(C_{1-4}alkyl_2)$ where $alkyl_1$ and $alkyl_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, -O-, $-S(O)_n-$, -NH-, $-NR_8-$, -C(=O)-, -C(=O)O-, -C(=O)NH-, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, NHC(=O)-, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;



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$R_7$ and $R_8$ are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_n$(alkyl), $-S(O)_n$(alkyl), $-S(O)_nNH$(alkyl), $-S(O)_nN(alkyl_3)(alkyl_4)$ where $alkyl_3$ and $alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo,



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hydroxy, amino, nitro, cyano, alkyl, alkoxy, haloalkyl, haloalkoxy, mono- or dialkylamino, and alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

5. (Previously Amended) A compound or salt according to Claim 4, wherein:

$R_A$, $R_B$, and $R_B'$ are independently selected at each occurrence from hydrogen and $C_{1-6}$alkyl;

each $R_3$ and $R_4$ is independently

(a) chosen from the group consisting of hydrogen, halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$; $C_{2-6}$alkynyl substituted with 0-2 $R_6$; $C_{1-6}$alkoxy substituted with 0-2 $R_6$, -NH($C_{1-6}$alkyl) substituted with 0-2 $R_6$, -N($C_{1-6}$alkyl)($C_{1-6}$alkyl) where each $C_{1-6}$alkyl is independently substituted with 0-2 $R_6$, $-XR_7$, and Y; or



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(b) joined to a $R_3$ or $R_4$ not attached to the same carbon to form an aryl ring substituted with 0-3 $R_6$, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 $R_6$, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is substituted with 0-2 $R_6$ and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

$R_7$ and $R_8$ are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)($C_{1-4}$alkyl), -N($C_{1-4}$alkyl)C(O)($C_{1-4}$alkyl), -NHS(O)$_n$($C_{1-4}$alkyl), -S(O)$_n$($C_{1-4}$alkyl), -S(O)$_n$NH($C_{1-4}$alkyl), -S(O)$_n$N($C_{1-4}$alkyl$_3$)($C_{1-4}$alkyl$_4$) where $C_{1-4}$alkyl$_3$



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and $C_{1-4}alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y'; and

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which are unsubstituted or substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo($C_{1-4}$)alkyl, halo($C_{1-4}$)alkoxy, mono- or di($C_{1-4}$)alkylamino, and $C_{1-4}$alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S.

6. (Original) A compound or salt according to Claim 4, wherein Z is oxygen.

7. (Cancelled)



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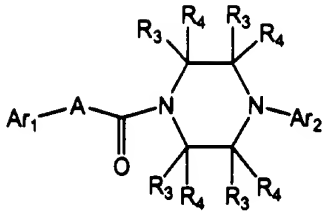
8. (Currently Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, $NR_A$, $CR_BR_B'$, $NR_ACR_BR_B'$, $CR_B\ R_B'NR_A$, $-CR_A=CR_B-$, and $C_3H_4$; where $R_A$, $R_B$, and $R_B'$ are independently selected at each occurrence from hydrogen or alkyl;

each $R_3$ and $R_4$ is independently

(a) selected from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; -COOH; -CHO, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted mono or dialkylamino; optionally substituted alkylthio; optionally substituted alkyl ketone; optionally substituted alkylester; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted mono- or di-alkylcarboxamide; optionally substituted $-S(O)_nNHalkyl$; optionally substituted $-S(O)_nN(alkyl)(alkyl)$; optionally substituted -NHC(=O)alkyl; optionally



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substituted -NC(=O)(alkyl)(alkyl); optionally substituted -NHS(O)$_n$alkyl; optionally substituted -NS(O)$_n$(alkyl)(alkyl); optionally substituted saturated heterocyclic ring or partially unsaturated heterocycle of from 5 to 8 atoms, which saturated heterocyclic ring or partially unsaturated heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; and optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring independently selected from the group consisting of N, O, and S; or

(b) joined to a $R_3$ or $R_4$ not attached to the same carbon to form an optionally substituted aryl ring; a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is optionally substituted; or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally substituted and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;



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$Ar_1$ [and $Ar_2$ are independently] is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl; wherein $Ar_1$ is optionally mono-, di-, or trisubstituted with $R_5$, and $Ar_2$ is optionally mono-, di-, or trisubstituted with $R_9$;

$Ar_2$ is selected from the group consisting of:

cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl; wherein $Ar_1$ is optionally



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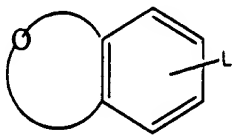
mono-, di-, or trisubstituted with $R_5$, and $Ar_2$ is optionally mono-, di-, or trisubstituted with $R_9$; and

(b) groups of the formula:




optionally mono-, di-, or trisubstituted with $R_5$, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

$R_5$ is independently selected at each occurrence from the group consisting of cyano, nitro, haloalkyl, haloalkoxy, hydroxy, amino, alkyl substituted with 0-2 $R_6$, alkenyl substituted with 0-2 $R_6$, alkynyl substituted with 0-2 $R_6$, alkoxy and Y;

$R_9$ is independently selected at each occurrence from the group consisting of nitro, haloalkoxy, hydroxy, amino, alkyl substituted with 0-2 $R_6$, alkenyl substituted with 0-2 $R_6$, alkynyl substituted with 0-2 $R_6$, alkoxy substituted with 0-2 $R_6$, and Y;

$R_6$ is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, alkyl,



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alkoxy, $-S(O)_n$(alkyl), haloalkyl, haloalkoxy, CO(alkyl), CONH(alkyl), CON(alkyl$_1$)(alkyl$_2$) where alkyl$_1$ and alkyl$_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, -O-, $-S(O)_n-$, -NH-, $-NR_8-$, -C(=O)-, -C(=O)O-, -C(=O)NH-, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, NHC(=O)-, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

$R_7$ and $R_8$ are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl),



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-NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_n(alkyl)$, $-S(O)_n(alkyl)$, $-S(O)_nNH(alkyl)$, $-S(O)_nN(alkyl_3)(alkyl_4)$ where $alkyl_3$ and $alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which are unsubstituted or substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, alkyl, alkoxy, haloalkyl, haloalkoxy, mono- or dialkylamino, and alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

9. (Previously Amended) A compound of the formula:



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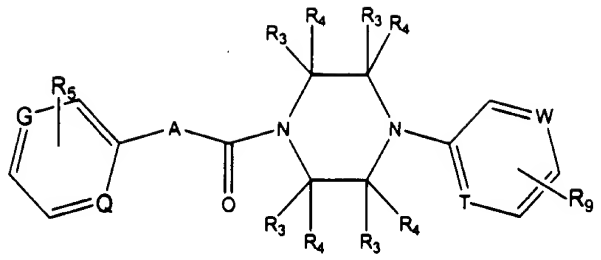

or a pharmaceutically acceptable salt thereof, wherein:

G, Q, T, and W are the same or different and are selected from the group consisting of N, CH, and $CR_5$, wherein T or W or both is N;

A is absent or is selected from the group consisting of O, S, $NR_A$, $CR_BR_B'$, $NR_ACR_BR_B'$, $CR_B\ R_B'NR_A$, $-CR_A=CR_B-$, and $C_3H_4$; where $R_A$, $R_B$, and $R_B'$ are independently selected at each occurrence from hydrogen and alkyl;

Z is oxygen or sulfur;

each $R_3$ and $R_4$ is independently

(a) selected from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; -COOH; -CHO, optionally substituted $C_{1-6}$alkyl; optionally substituted $C_{2-6}$alkenyl; optionally substituted $C_{2-6}$alkynyl; optionally substituted $C_{1-6}$alkoxy; optionally substituted mono or di($C_{1-6}$)alkylamino; optionally substituted $C_{1-6}$alkylthio; optionally substituted $C_{1-6}$alkyl ketone; optionally substituted $C_{1-6}$alkylester; optionally substituted $C_{1-}$



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$_6$alkylsulfinyl; optionally substituted $C_1$-$_6$alkylsulfonyl; optionally substituted mono- or di($C_1$-$_6$)alkylcarboxamide; optionally substituted -S(O)$_n$NH $C_1$-$_6$alkyl; optionally substituted -S(O)$_n$N($C_{1-6}$alkyl)($C_1$-$_6$alkyl); optionally substituted -NHC(=O) $C_{1-6}$alkyl; optionally substituted -NC(=O)($C_{1-6}$alkyl)($C_{1-6}$alkyl); optionally substituted -NHS(O)$_n$$C_{1-6}$alkyl; optionally substituted -NS(O)$_n$($C_{1-6}$alkyl)($C_{1-6}$alkyl); optionally substituted saturated heterocyclic ring or partially unsaturated heterocycle of from 5 to 8 atoms, which saturated heterocyclic ring or partially unsaturated heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; and optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring independently selected from the group consisting of N, O, and S; or

(b) joined to a $R_3$ or $R_4$ not attached to the same carbon to form an optionally substituted aryl ring; a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is



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optionally substituted; or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally substituted and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

$R_5$ represents 1 to 3 substituents independently selected at each occurrence from the group consisting of cyano, hydroxy, amino, $C_{3-6}$ alkyl substituted with 0-2 $R_6$, $C_{2-6}$ alkenyl substituted with 0-2 $R_6$, $C_{2-6}$ alkynyl substituted with 0-2 $R_6$, $C_{3-6}$ alkoxy, $-NH(C_{1-6}alkyl)$ substituted with 0-2 $R_6$, $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$ where each alkyl is independently substituted with 0-2 $R_6$, $-XR_7$, and Y;

$R_9$ represents 0 to 3 substituents independently selected at each occurrence from the group consisting of halogen, nitro, $halo(C_{1-6})alkyl$, $halo(C_{1-6})alkoxy$, hydroxy, amino, $C_{1-6}alkyl$ substituted with 0-2 $R_6$, $C_{2-6}alkenyl$ substituted with 0-2 $R_6$, $C_{2-6}alkynyl$ substituted with 0-2 $R_6$, $C_{1-6}alkoxy$ substituted with 0-2 $R_6$, and Y;

$R_6$ is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $-S(O)_n(C_{1-4}alkyl)$, $halo(C_{1-4})alkyl$, $halo(C_{1-4})alkoxy$, $CO(C_{1-4}alkyl)$, $CONH(C_{1-4}alkyl)$, $CON(C_{1-}$



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$_4$alkyl$_1$)($C_{1-4}$alkyl$_2$) where alkyl$_1$ and alkyl$_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, -O-, $-S(O)_n-$, -NH-, $-NR_8-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)NH-$, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, $NHC(=O)-$, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

$R_7$ and $R_8$ are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, $-O(C_{1-4}alkyl)$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-NHS(O)_n(C_{1-4}alkyl)$, $-S(O)_n(C_{1-}$



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$_4$alkyl), $-S(O)_nNH(C_{1-4}alkyl)$, $-S(O)_nN(C_{1-4}alkyl_3)(C_{1-4}alkyl_4)$ where $C_{1-4}alkyl_3$ and $C_{1-4}alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which are unsubstituted or substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, oyano, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo($C_{1-4}$)alkyl, halo($C_{1-4}$)alkoxy, mono- or di($C_{1-4}$)alkylamino, and $C_{1-4}$alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

10. (Original) A compound according to Claim 9, which is 4-(3-Chloro-2-pyridinyl)-N-[4(isopropyl)phenyl]-2-



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methylthio-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

11. (Original) A compound according to Claim 9, wherein $R_3$ and $R_4$ are independently selected at each occurrence from the group consisting of hydrogen and $C_{1-6}$ alkyl.

12. (Original) A compound according to Claim 11, wherein G and Q are selected from the group consisting of CH and $CR_5$.

13. (Original) A compound according to Claim 11, wherein G , Q, and W are independently selected at each occurrence from the group consisting of CH and $CR_5$; and T is N.

14. (Original) A compound according to Claim 13 wherein $R_3$ and $R_4$ are hydrogen; and A is selected from the group consisting of NH, -CH=CH-, and $-CH_2NH-$.

15. (Original) A compound or salt according to Claim 14, wherein $R_6$ is independently selected at each occurrence



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from the group consisting of halogen, hydroxy, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, -NH($C_{1-4}$alkyl), and -N($C_{1-4}$ alkyl)($C_{1-4}$ alkyl).

16. (Original) A compound according to Claim 14, which is 4-(3-Trifluoromethyl-2-pyridinyl)-N-(3-methoxy-4-hydroxyphenylmethyl)-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

17. (Original) A compound according to Claim 14, which is 4-(3-Nitro-pyridinyl)-N-[4-(n-butyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

18. (Original) A compound according to Claim 14, which is 4-(3-Trifluoromethyl-2-pyridinyl)-N-[4-(n-butyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

19. (Original) A compound according to Claim 14, which is 4-(3-Methyl-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.



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20. (Original) A compound according to Claim 14, which is 4-(3-Methyl-2-pyridinyl)-N-[4-(n-butyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

21. (Original) A compound according to Claim 14, which is 4-(3-Chloro-5-trifluoromethyl-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

22. (Original) A compound according to Claim 14, which is 4-(3-Chloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

23. (Original) A compound according to Claim 14, which is 4-(3,5-Dichloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

24. (Original) A compound according to claim 13, which is 4-(3-Cyano-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-



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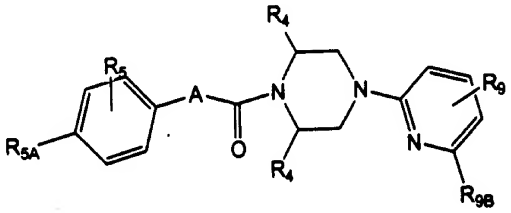
piperazinecarboxamide, or a pharmaceutically acceptable salt thereof.

25. (Original) The compound according to claim 13, which is 4-(3-Chloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-2-methyl-1-piperazinecarboxamide.

26. (Previously Amended) A compound of the formula:




or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of NH, -CH=CH-, and $CH_2NH$;

$R_4$ is independently chosen from hydrogen and $C_{1-4}$ alkyl;

$R_5$ represents 0 to 2 substituents independently chosen at each occurrence from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$, $C_{2-6}$alkynyl substituted with 0-2 $R_6$, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl) substituted with 0-2 $R_6$, and -N($C_{1-6}$alkyl)( $C_{1-6}$alkyl)



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where each $C_{1-6}$alkyl is independently substituted with 0-2 $R_6$;

$R_9$ represents 0 to 2 substituents and is independently chosen at each occurrence from the group consisting of halogen, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$, $C_{2-6}$alkynyl substituted with 0-2 $R_6$, and $C_{1-6}$alkoxy substituted with 0-2 $R_6$.

$R_{5A}$ is independently selected from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, -NH($C_{1-6}$ alkyl), and -N($C_{1-6}$ alkyl)($C_{1-6}$ alkyl);

$R_{9B}$ is independently selected from the group consisting of halogen, nitro, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$ alkyl, and $C_{1-6}$ alkoxy; and

$R_6$ is independently selected at each occurrence the group consisting of halogen, hydroxy, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, -NH($C_{1-4}$ alkyl), and -N($C_{1-4}$ alkyl)($C_{1-4}$ alkyl).



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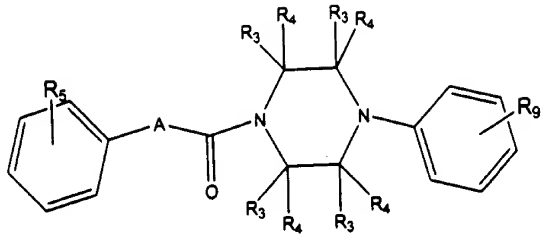
27. (Previously Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of a single bond, S, $NR_A$, $NR_ACHR_B$, $CHR_BNR_A$, $-CR_A=CR_B-$, and $C_3H_4$; where $R_A$ and $R_B$ are independently selected at each occurrence from the group consisting of hydrogen and alkyl;

each $R_3$ and $R_4$ is independently

(a) selected from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; -COOH; -CHO, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted mono or dialkylamino; optionally substituted alkylthio; optionally substituted alkyl ketone; optionally substituted alkylester; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted mono- or di-alkylcarboxamide; optionally substituted $-S(O)_nNH$alkyl; optionally substituted $-S(O)_nN$(alkyl)(alkyl);



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optionally substituted -NHC(=O)alkyl; optionally substituted -NC(=O)(alkyl)(alkyl); optionally substituted -NHS(O)$_n$alkyl; optionally substituted -NS(O)$_n$(alkyl)(alkyl); optionally substituted saturated heterocyclic ring or partially unsaturated heterocycle of from 5 to 8 atoms, which saturated heterocyclic ring or partially unsaturated heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; and optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring independently selected from the group consisting of N, O, and S; or

(b) joined to a $R_3$ or $R_4$ not attached to the same carbon to form an optionally substituted aryl ring; a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is optionally substituted; or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally



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substituted and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

$R_5$ represents 0-3 substituents independently selected at each occurrence from the group consisting of cyano, nitro, haloalkyl, haloalkoxy, $C_{2-6}$ alkenyl substituted with 0-2 $R_6$, and $C_{2-6}$ alkynyl substituted with 0-2 $R_6$;

$R_9$ represents 0-3 substituents independently selected at each occurrence from the group consisting of bromo, haloalkyl, haloalkoxy, hydroxy, $C_{2-6}$ alkyl substituted with 0-2 $R_6$, $C_{2-6}$ alkenyl substituted with 0-2 $R_6$, $C_{2-6}$ alkynyl substituted with 0-2 $R_6$, and $C_{2-6}$ alkoxy;

$R_6$ is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, alkyl, alkoxy, $-S(O)_n(alkyl)$, haloalkyl, haloalkoxy, $CO(alkyl)$, $CONH(alkyl)$, $CON(alkyl_1)(alkyl_2)$ where $alkyl_1$ and $alkyl_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, $-O-$, $-S(O)_n-$, $-NH-$, $-NR_8-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)NH-$, $-C(=O)NR_8-$, $-S(O)_nNH-$,



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$-S(O)_nNR_8-$, $NHC(=O)-$, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

$R_7$ and $R_8$ are independently selected at each occurrence from straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 3 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 3 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_n$(alkyl), $-S(O)_n$(alkyl), $-S(O)_nNH$(alkyl), $-S(O)_nN(alkyl_3)(alkyl_4)$ where $alkyl_3$ and $alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which are unsubstituted or substituted with one or more



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substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, alkyl, alkoxy, haloalkyl, haloalkoxy, mono- or dialkylamino, and alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

28. (Original) A compound or salt according to Claim 27 in which $R_3$ and $R_4$ are independently selected at each occurrence from the group consisting of hydrogen and $C_{1-6}$ alkyl.

29. (Original) A compound or salt according to claim 27, wherein A is selected from the group consisting of NH, -CH=CH-, and $CH_2NH$; $R_3$ is hydrogen and $R_4$ is independently chosen at each occurrence from hydrogen and methyl; and $R_6$ is independently selected at each occurrence from the group consisting of halogen, hydroxy, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, -NH($C_{1-4}$ alkyl), and -N($C_{1-4}$ alkyl)($C_{1-4}$ alkyl).



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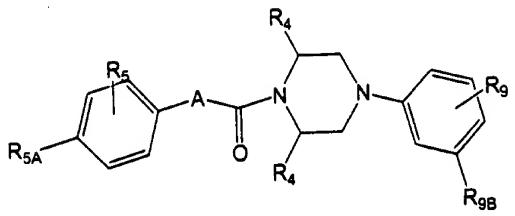
30. (Previously Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of NH, -CH=CH-, and $CH_2NH$;

$R_4$ is independently selected at each occurrence from hydrogen and $C_{1-4}$alkyl;

$R_5$ represents 0 to 2 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, amino, $C_{2-6}$alkenyl substituted with 0-2 $R_6$, and $C_{2-6}$alkynyl substituted with 0-2 $R_6$;

$R_9$ represents 0 to 2 substituents and is independently selected at each occurrence from the group consisting of halogen, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$, $C_{2-6}$alkynyl substituted with 0-2 $R_6$, and $C_{1-6}$alkoxy substituted with 0-2 $R_6$;

$R_{5A}$ is independently selected from the group consisting of halogen, cyano, nitro, trifluoromethyl,



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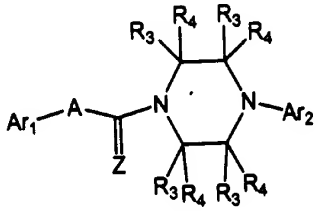
trifluoromethoxy, hydroxy, amino, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, -NH($C_{1-6}$ alkyl), and -N($C_{1-6}$ alkyl)($C_1$-$C_6$ alkyl);

$R_{9B}$ is independently selected from the group consisting of trifluoromethoxy, hydroxy, $C_{2-6}$ alkyl, and $C_{2-6}$ alkoxy; and

$R_6$ is independently selected at each occurrence from the group consisting of halogen, hydroxy, $C_{1-4}$ alkyl, and $C_{1-4}$ alkoxy.

31. (Previously Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein the compound or pharmaceutically acceptable salt thereof exhibits an EC50 or $K_i$ of 1 micromolar or less in a standard assay of capsaicin receptor mediated calcium mobilization; and wherein

A is absent or is selected from the group consisting of O, S, $NR_A$, $NR_ACR_BR_B'$, $CR_B$ $R_B'NR_A$, $-CR_A=CR_B-$, and $C_3H_4$; where $R_A$, $R_B$, and $R_B'$ are independently selected at each occurrence from hydrogen and $C_{1-6}$ alkyl;

Z is oxygen or sulfur;



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each $R_3$ and $R_4$ is independently

(a) selected from the group consisting of hydrogen, halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$; $C_{2-6}$alkynyl substituted with 0-2 $R_6$; $C_{1-6}$alkoxy substituted with 0-2 $R_6$, -NH($C_{1-6}$alkyl) substituted with 0-2 $R_6$, -N($C_{1-6}$alkyl)($C_{1-6}$alkyl) where each $C_{1-6}$alkyl is independently substituted with 0-2 $R_6$, -$XR_7$, and Y; or

(b) joined to a $R_3$ or $R_4$ not attached to the same carbon to form an aryl ring substituted with 0-3 $R_6$, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 $R_6$, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is substituted with 0-2 $R_6$ and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

$Ar_1$ is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl,



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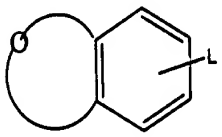
pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with $R_5$; and

(b) bicyclic oxygen-containing groups of the formula:




optionally mono-, di-, or trisubstituted with $R_5$, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

$Ar_2$ is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, [pyrazinyl,] benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl,



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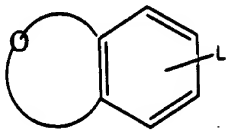
isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with $R_5$; and

(b) bicyclic oxygen-containing groups of the formula:




optionally mono-, di-, or trisubstituted with $R_5$, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

$R_5$ is independently selected at each occurrence from the group consisting of halogen, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$, $C_{2-6}$alkynyl substituted with 0-2 $R_6$, $C_{1-6}$alkoxy and Y;

$R_6$ is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $-S(O)_n(C_{1-4}$alkyl), halo($C_{1-4}$)alkyl, halo($C_{1-4}$)alkoxy, $CO(C_{1-4}$alkyl), $CONH(C_{1-4}$alkyl), $CON(C_{1-4}$



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$_4$alkyl$_1$)($C_{1-4}$alkyl$_2$) where alkyl$_1$ and alkyl$_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, $-O-$, $-S(O)_n-$, $-NH-$, $-NR_8-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)NH-$, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, $NHC(=O)-$, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

$R_7$ and $R_8$ are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, $-O(C_{1-4}alkyl)$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-NHS(O)_n(C_{1-4}alkyl)$, $-S(O)_n(C_{1-}$



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$_4$alkyl), $-S(O)_nNH(C_{1-4}alkyl)$, $-S(O)_nN(C_{1-4}alkyl_3)(C_{1-4}alkyl_4)$ where $C_{1-4}alkyl_3$ and $C_{1-4}alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo($C_{1-4}$)alkyl, halo($C_{1-4}$)alkoxy, mono- or di($C_{1-4}$)alkylamino, and $C_{1-4}$alkylthio;

wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

32. (Previously Amended) A compound of the Formula A, Formula B, Formula C, Formula D, Formula E, or Formula F:



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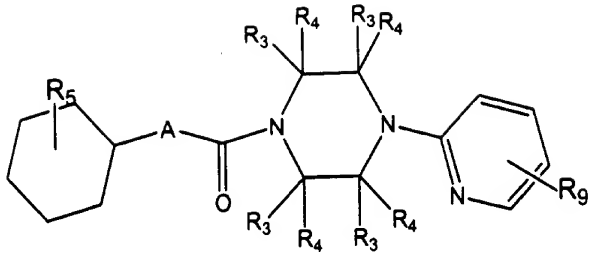
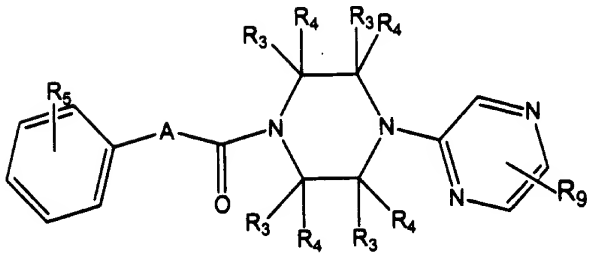
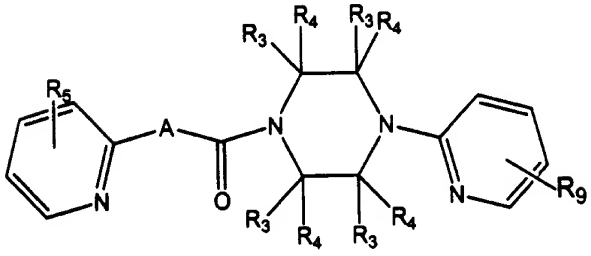


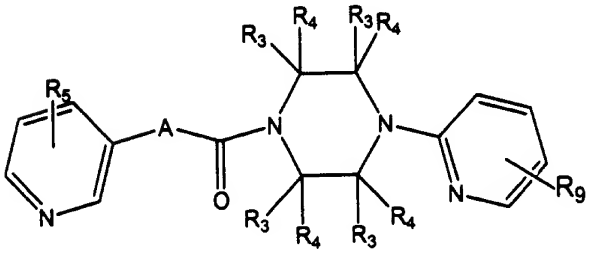
Formula A



Formula B



Formula C



Formula D



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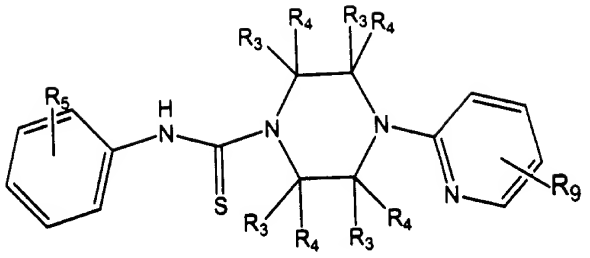
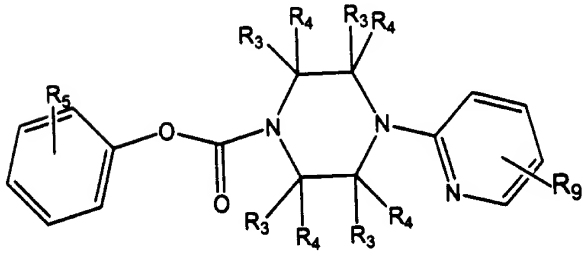


**Formula E**



**Formula F**

or a pharmaceutically acceptable salt of Formula A, Formula B, Formula C, Formula D, Formula E, or Formula F, wherein

A represents NH or O;

each $R_3$ and $R_4$ is independently

(a) selected from the group consisting of hydrogen, halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$; $C_{2-6}$alkynyl substituted with 0-2 $R_6$; $C_{1-6}$alkoxy substituted with 0-2 $R_6$, -NH($C_{1-6}$alkyl) substituted with 0-2 $R_6$, -N($C_{1-}$



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$_6$alkyl)($C_{1-6}$alkyl) where each $C_{1-6}$alkyl is independently substituted with 0-2 $R_6$, -$XR_7$, and Y; or

(b) joined to a $R_3$ or $R_4$ not attached to the same carbon to form an aryl ring substituted with 0-3 $R_6$, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 $R_6$, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is substituted with 0-2 $R_6$ and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

$R_5$ represents from 1 to 3 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$, $C_{2-6}$alkynyl substituted with 0-2 $R_6$, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl) substituted with 0-2 $R_6$, -N($C_{1-6}$alkyl)($C_{1-6}$alkyl) where each $C_{1-6}$alkyl is independently substituted with 0-2 $R_6$, -$XR_7$, and Y;

$R_9$ represents from 1 to 3 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-}$



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$_6$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$, $C_{2-6}$alkynyl substituted with 0-2 $R_6$, $C_{1-6}$alkoxy substituted with 0-2 $R_6$, and Y;

$R_6$ is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $-S(O)_n(C_{1-4}alkyl)$, halo($C_{1-4}$)alkyl, halo($C_{1-4}$)alkoxy, $CO(C_{1-4}alkyl)$, $CONH(C_{1-4}alkyl)$, $CON(C_{1-4}alkyl_1)(C_{1-4}alkyl_2)$ where $alkyl_1$ and $alkyl_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, -O-, $-S(O)_n-$, -NH-, $-NR_8-$, -C(=O)-, -C(=O)O-, -C(=O)NH-, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, NHC(=O)-, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

$R_7$ and $R_8$ are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon



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atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O($C_{1-4}$alkyl), -NH($C_{1-4}$alkyl), -N($C_{1-4}$alkyl)($C_{1-4}$alkyl), -NHC(O)($C_{1-4}$alkyl), -N($C_{1-4}$alkyl)C(O)($C_{1-4}$alkyl), -NHS(O)$_n$($C_{1-4}$alkyl), -S(O)$_n$($C_{1-4}$alkyl), -S(O)$_n$NH($C_{1-4}$alkyl), -S(O)$_n$N($C_{1-4}$alkyl$_3$)($C_{1-4}$alkyl$_4$) where $C_{1-4}$alkyl$_3$ and $C_{1-4}$alkyl$_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo($C_{1-4}$)alkyl, halo($C_{1-4}$)alkoxy, mono- or di($C_{1-4}$)alkylamino, and $C_{1-4}$alkylthio;



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wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

33. (Original) A compound or salt according to Claim 32, wherein A represents NH.

34. (Original) A compound or salt according to Claim 32, wherein:

A represents NH; and

$R_3$ and $R_4$ are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy substituted with 0-2 $R_6$, -NH($C_{1-6}$alkyl), and -N($C_{1-6}$alkyl)($C_{1-6}$alkyl).

35. (Original) A compound or salt according to Claim 32, wherein:

A represents NH;

$R_3$ represents hydrogen; and



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$R_4$ is independently chosen at each occurrence from hydrogen and $C_{1-6}$ alkyl.

36. (Original) A compound or salt according to Claim 32, wherein:

A represents NH;

$R_3$ represents hydrogen; and

$R_4$ is independently chosen at each occurrence from hydrogen and methyl.

37. (Previously Amended) A compound or salt according to Claim 32, wherein:

A represents NH;

$R_3$ represents hydrogen;

$R_4$ is independently chosen at each occurrence from hydrogen and methyl; and

$R_5$ represents from 1 to 3 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl), -N($C_{1-6}$alkyl)($C_{1-6}$alkyl), and $C_{3-8}$ cycloalkyl; and



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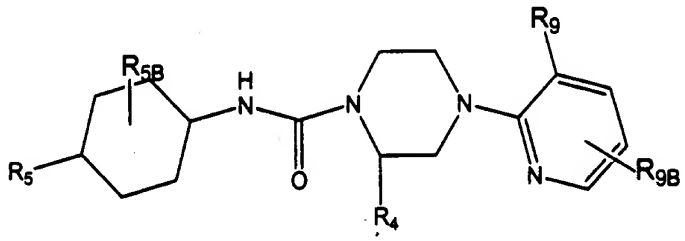
$R_9$ represents from 1 to 3 substituents independently selected at each occurrence from the group consisting of halogen, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, and $C_{3-8}$ cycloalkyl.

38. (Previously Amended) A compound or salt of the Formula A-1




**Formula A-1**

wherein

$R_4$ is hydrogen or methyl;

$R_5$ and $R_9$ are independently selected from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl), -N($C_{1-6}$alkyl)($C_{1-6}$alkyl), and $C_{3-8}$ cycloalkyl; and

$R_{5B}$ and $R_{9B}$ each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo($C_{1-2}$)alkyl,



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halo($C_{1-2}$)alkoxy, hydroxy, amino, $C_{1-3}$alkyl, $C_{1-3}$alkoxy, -NH($C_{1-3}$alkyl), and -N($C_{1-6}$alkyl)($C_{1-6}$alkyl).

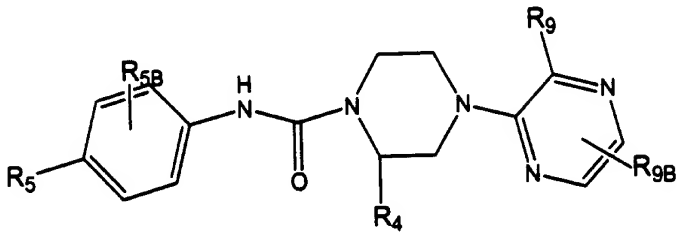
39. (Original) A compound or salt according to Claim 38, wherein:

$R_5$ is $C_{3-6}$ alkyl; $C_{3-6}$ alkoxy; halo($C_{1-3}$)alkyl, halo($C_{1-3}$)alkoxy, or $C_{3-8}$ cycloalkyl;

$R_9$ is chloro or trifluoromethyl; and

$R_{5B}$ and $R_{9B}$ are hydrogen.

40. (Previously Amended) A compound or salt of Formula B-1




**Formula B-1**

wherein

$R_4$ is hydrogen or methyl;

$R_5$ and $R_9$ are independently selected from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl,



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$C_{2-6}$alkynyl, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl), -N($C_{1-6}$alkyl)($C_{1-6}$alkyl), and $C_{3-8}$ cycloalkyl; and

$R_{5B}$ and $R_{9B}$ each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, hydroxy, amino, $C_{1-3}$alkyl, $C_{1-3}$alkoxy, -NH($C_{1-3}$alkyl), and -N($C_{1-6}$alkyl)($C_{1-6}$alkyl).

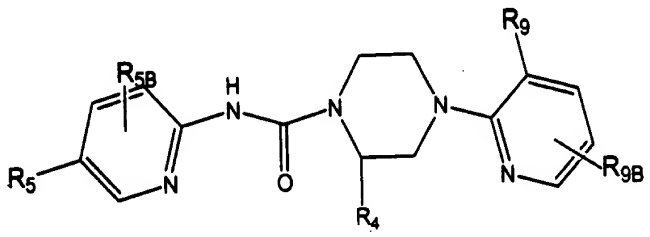
41. (Original) A compound or salt according to Claim 40, wherein:

$R_5$ is $C_{3-6}$ alkyl; $C_{3-6}$ alkoxy; halo($C_{1-3}$)alkyl, halo($C_{1-3}$)alkoxy, or $C_{3-8}$ cycloalkyl;

$R_9$ is chloro or trifluoromethyl; and

$R_{5B}$ and $R_{9B}$ are hydrogen.

42. (Previously Amended) A compound or salt of Formula C-1




**Formula C-1**

wherein:



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$R_4$ is hydrogen or methyl;

$R_5$ and $R_9$ are independently selected from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl), -N($C_{1-6}$alkyl)($C_{1-6}$alkyl), and $C_{3-8}$ cycloalkyl; and

$R_{5B}$ and $R_{9B}$ each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, hydroxy, amino, $C_{1-3}$alkyl, $C_{1-3}$alkoxy, -NH($C_{1-3}$alkyl), and -N($C_{1-6}$alkyl)($C_{1-6}$alkyl).

43. (Original) A compound or salt according to Claim 42, wherein:

$R_5$ is $C_{3-6}$ alkyl; $C_{3-6}$ alkoxy; halo($C_{1-3}$)alkyl, halo($C_{1-3}$)alkoxy, or $C_{3-8}$ cycloalkyl;

$R_9$ is chloro or trifluoromethyl; and

$R_{5B}$ and $R_{9B}$ are hydrogen.

44. (Previously Amended) A compound or salt according to Claim 37 of Formula D-1



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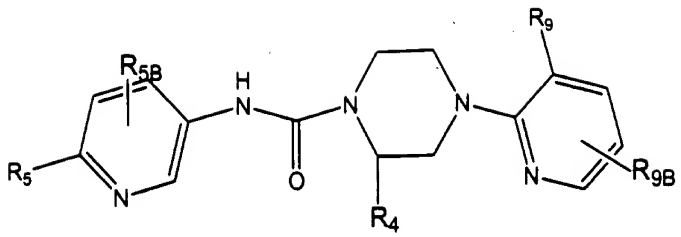

**Formula D-1**

wherein:

$R_5$ is selected from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl), -N($C_{1-6}$alkyl)($C_{1-6}$alkyl), and $C_{3-8}$ cycloalkyl;

$R_9$ is selected from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, and $C_{3-8}$ cycloalkyl; and

$R_{5B}$ and $R_{9B}$ each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, hydroxy, amino, $C_{1-3}$alkyl, $C_{1-3}$alkoxy, -NH($C_{1-3}$alkyl), and -N($C_{1-6}$alkyl)($C_{1-6}$alkyl).

45. (Original) A compound or salt according to Claim 44, wherein:



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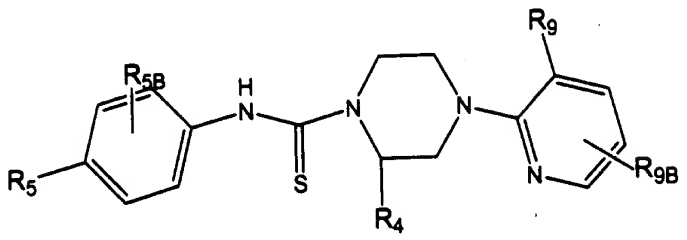
$R_5$ is $C_{3-6}$ alkyl; $C_{3-6}$ alkoxy; halo($C_{1-3}$)alkyl, halo($C_{1-3}$)alkoxy, or $C_{3-8}$ cycloalkyl;

$R_9$ is chloro or trifluoromethyl; and

$R_{5B}$ and $R_{9B}$ are hydrogen.

46. (Previously Amended) A compound or salt of Formula E-1




**Formula E-1**

wherein:

$R_4$ is hydrogen or methyl;

$R_5$ and $R_9$ are independently selected from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl), -N($C_{1-6}$alkyl)($C_{1-6}$alkyl), and $C_{3-8}$ cycloalkyl; and

$R_{5B}$ and $R_{9B}$ each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo($C_{1-2}$)alkyl,



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halo($C_{1-2}$)alkoxy, hydroxy, amino, $C_{1-3}$alkyl, $C_{1-3}$alkoxy, -NH($C_{1-3}$alkyl), and -N($C_{1-6}$alkyl)($C_{1-6}$alkyl).

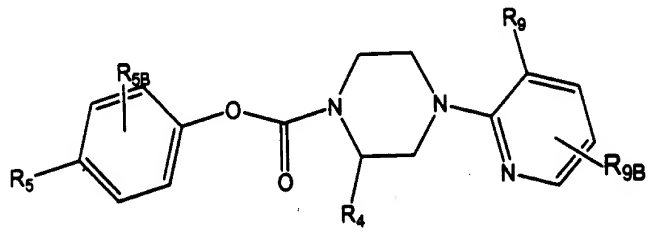
47. (Original) A compound or salt according to Claim 46, wherein:

$R_5$ is $C_{3-6}$ alkyl; $C_{3-6}$ alkoxy; halo($C_{1-3}$)alkyl, halo($C_{1-3}$)alkoxy, or $C_{3-8}$ cycloalkyl;

$R_9$ is chloro or trifluoromethyl; and

$R_{5B}$ and $R_{9B}$ are hydrogen.

48. (Previously Amended) A compound of salt of Formula F-1




**Formula F-1**

wherein:

$R_4$ is hydrogen or methyl;

$R_5$ and $R_9$ are independently selected from the group consisting of halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl), -N($C_{1-6}$alkyl)( $C_{1-6}$alkyl), and $C_{3-8}$ cycloalkyl; and



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$R_{5B}$ and $R_{9B}$ each represent from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, hydroxy, amino, $C_{1-3}$alkyl, $C_{1-3}$alkoxy, -NH($C_{1-3}$alkyl), and -N($C_{1-6}$alkyl)($C_{1-6}$alkyl).

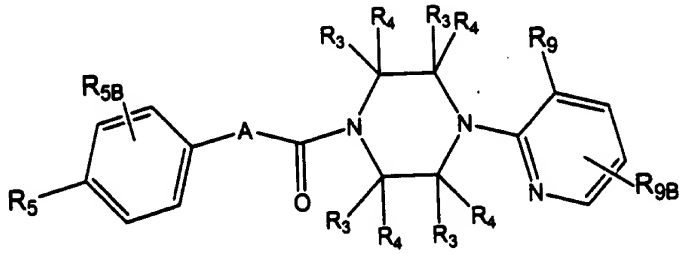
49. (Original) A compound or salt according to Claim 47, wherein:

$R_5$ is $C_{3-6}$ alkyl; $C_{3-6}$ alkoxy; halo($C_{1-3}$)alkyl, halo($C_{1-3}$)alkoxy, or $C_{3-8}$ cycloalkyl;

$R_9$ is chloro or trifluoromethyl; and

$R_{5B}$ and $R_{9B}$ are hydrogen.

50. (Previously Amended) A compound of the Formula:




or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, $NR_A$, $CR_BR_B'$, $NR_ACR_BR_B'$, $CR_B$ $R_B'NR_A$, -$CR_A$=$CR_B$-, and $C_3H_4$; where $R_A$, $R_B$, and $R_B'$ are independently selected at each occurrence from hydrogen and $C_{1-6}$ alkyl;



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each $R_3$ and $R_4$ is independently

(a) selected from the group consisting of hydrogen, halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$; $C_{2-6}$alkynyl substituted with 0-2 $R_6$; $C_{1-6}$alkoxy substituted with 0-2 $R_6$, -NH($C_{1-6}$alkyl) substituted with 0-2 $R_6$, -N($C_{1-6}$alkyl)($C_{1-6}$alkyl) where each $C_{1-6}$alkyl is independently substituted with 0-2 $R_6$, $-XR_7$, and Y; or

(b) joined to a $R_3$ or $R_4$ not attached to the same carbon to form an aryl ring substituted with 0-3 $R_6$, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 $R_6$, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is substituted with 0-2 $R_6$ and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

$R_5$ is selected from the group consisting of bromo, fluoro, iodo, halo($C_{1-6}$)alkyl, halo($C_{3-6}$)alkoxy, $C_{3-6}$alkyl substituted with 0-3 $R_6$, $C_{2-6}$alkenyl substituted with 0-3 $R_6$, $C_{2-6}$alkynyl substituted with 0-3 $R_6$, $C_{3-6}$alkoxy, ($C_{3-8}$cycloalkyl)$C_{1-4}$alkyl, -NH($C_{1-6}$alkyl) substituted



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with 0-2 $R_6$, -N($C_{1-6}$alkyl)($C_{1-6}$alkyl) where each $C_{1-6}$alkyl is substituted with 0-2 $R_6$, Y, -(C=O)Y, -($CH_2$)Y, and -(CH(CN))Y;

$R_9$ is selected from the group consisting of halogen, cyano, -N($SO_2C_{1-6}$alkyl)($SO_2C_{1-6}$alkyl), -$SO_2NH_2$, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, $C_{1-6}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$, $C_{2-6}$alkynyl substituted with 0-2 $R_6$, and $C_{1-6}$alkoxy substituted with 0-2 $R_6$;

$R_{5B}$ represents from 0 to 2 substituents independently selected at each occurrence from the group consisting of

(a) halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, ($C_{3-8}$cycloalkyl)$C_{1-4}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$, $C_{2-6}$alkynyl substituted with 0-2 $R_6$, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl) substituted with 0-2 $R_6$, -N($C_{1-6}$alkyl)($C_{1-6}$alkyl) where each $C_{1-6}$alkyl is independently substituted with 0-2 $R_6$, and Y; and

(b) groups that are joined to $R_5$ to form a $C_{3-8}$cycloalkyl group or a saturated heterocyclic ring or partially unsaturated heterocycle, each of which is optionally



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substituted by from 1 to 5 substituents independently chosen from cyano, halogen, hydroxy, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, -NH($C_{1-4}$alkyl), -N($C_{1-4}$alkyl)($C_{1-4}$alkyl), halo($C_{1-4}$)alkyl, and halo($C_{1-4}$)alkoxy, wherein the saturated heterocyclic ring or partially unsaturated heterocycle contains from 4 to 8 ring atoms of which 1, 2, or 3 are heteroatoms independently selected from N, O, and S;

$R_{9B}$ represents from 0 to 2 substituents independently selected at each occurrence from halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl substituted with 0-2 $R_6$, ($C_{3-8}$cycloalkyl)$C_{1-4}$alkyl substituted with 0-2 $R_6$, $C_{2-6}$alkenyl substituted with 0-2 $R_6$, $C_{2-6}$alkynyl substituted with 0-2 $R_6$, $C_{1-6}$alkoxy substituted with 0-2 $R_6$, and Y;

$R_6$ is independently selected at each occurrence from the group consisting of cyano, halogen, hydroxy, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, -S(O)$_n$($C_{1-4}$alkyl), halo($C_{1-4}$)alkyl, halo($C_{1-4}$)alkoxy, CO($C_{1-4}$alkyl), CONH($C_{1-4}$alkyl), CON($C_{1-4}$alkyl$_1$)($C_{1-4}$alkyl$_2$) where alkyl$_1$ and alkyl$_2$ may be joined to form a saturated heterocyclic ring [heterocycle] of from 5 to 8 ring atoms and containing 1, 2, or 3



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heteroatoms independently selected from N, O, and S, -$XR_7$, and Y;

X is independently selected at each occurrence from the group consisting of -$CH_2$-, -$CHR_8$-, -O-, -$S(O)_n$-, -NH-, -$NR_8$-, -C(=O)-, -C(=O)NH-, -$C(=O)NR_8$-, -$S(O)_n$NH-, -$S(O)_nNR_8$-, NHC(=O)-, -$NR_8C(=O)$-, -$NHS(O)_n$-, and -$NR_8S(O)_n$-;

$R_7$ and $R_8$ are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms may be further substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O($C_{1-4}$alkyl), NH($C_{1-4}$alkyl), -N($C_{1-4}$alkyl)( $C_{1-4}$alkyl), -NHC(O)( $C_{1-4}$alkyl), -N($C_{1-4}$alkyl)C(O)( $C_{1-4}$alkyl), -$NHS(O)_n$($C_{1-4}$alkyl), -$S(O)_n$($C_{1-4}$alkyl), -$S(O)_n$NH($C_{1-4}$alkyl), -$S(O)_n$N($C_{1-4}$$alkyl_3$)( $C_{1-4}$$alkyl_4$) where $C_{1-4}$$alkyl_3$ and $C_{1-4}$$alkyl_4$ are optionally joined to form a saturated heterocyclic ring [heterocycle] consisting of from 5



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to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo($C_{1-4}$)alkyl, halo($C_{1-4}$)alkoxy, mono- or di($C_{1-4}$)alkylamino, and $C_{1-4}$alkylthio;wherein said 3- to 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

51. (Original) A compound or salt according to Claim 50, wherein:

A is O or $NR_A$, wherein $R_A$ is hydrogen or methyl.

52. (Original) A compound or salt according to Claim 50, wherein:

A is O or $NR_A$, wherein $R_A$ is hydrogen or methyl; and



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$R_3$ and $R_4$ are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl), and -N($C_{1-6}$alkyl)($C_{1-6}$alkyl).

53. (Original) A compound or salt according to Claim 50, wherein:

A is O or $NR_A$, wherein $R_A$ is hydrogen or methyl;

$R_3$ is hydrogen; and

$R_4$ is independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl), and -N($C_{1-6}$alkyl)($C_{1-6}$alkyl).

54. (Original) A compound or salt according to Claim 50, wherein:

A is O or $NR_A$, wherein $R_A$ is hydrogen or methyl;

$R_3$ is hydrogen; and

$R_4$ is independently chosen at each occurrence from hydrogen and $C_{1-6}$alkyl.



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55. (Original) A compound or salt according to Claim 50, wherein:

A is $NR_A$, wherein $R_A$ is hydrogen or methyl;

$R_3$ is hydrogen; and

$R_4$ is independently chosen at each occurrence from hydrogen, halo($C_{1-3}$)alkyl, and $C_{1-6}$alkyl.

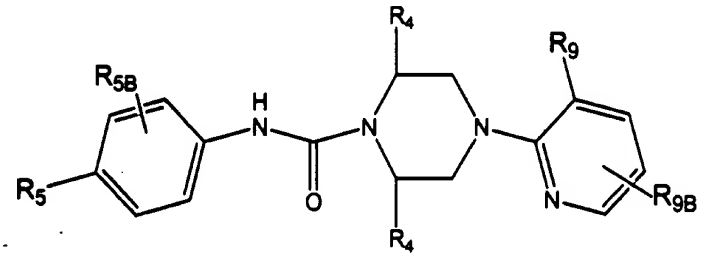
56. (Original) A compound or salt according to Claim 50, wherein:

A is $NR_A$, wherein $R_A$ is hydrogen or methyl;

$R_3$ is hydrogen; and

$R_4$ is independently chosen at each occurrence from hydrogen and $C_{1-4}$alkyl.

57. (Original) A compound or salt according to Claim 50 of the Formula




wherein:

$R_4$ is independently chosen at each occurrence from hydrogen and $C_{1-4}$alkyl.



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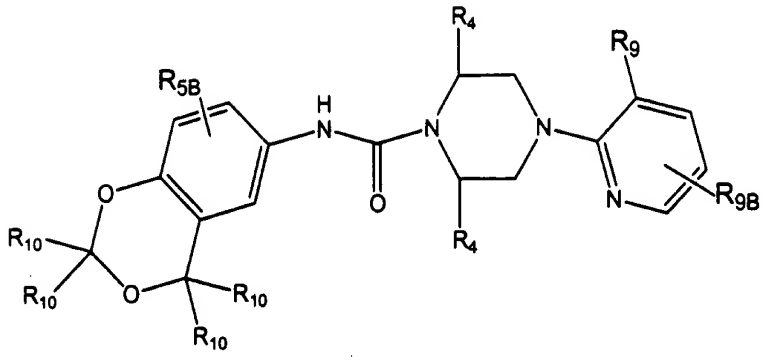
58. (Original) A compound or salt according to Claim 57 of the formula:




wherein

$R_{5B}$ and $R_{9B}$ are independently chosen from hydrogen, halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, amino, $C_{1-4}$alkyl, and $C_{1-2}$alkoxy; and

$R_{10}$ is independently chosen at each occurrence from hydrogen, halogen, and $C_{1-4}$ alkyl.

59. (Previously Amended) A compound or salt according to Claim 58 wherein:

$R_9$ is selected from the group consisting of halogen, cyano, $-N(SO_2CH_3)_2$, $-SO_2NH_2$, halo($C_{1-3}$)alkyl, and $C_{1-3}$alkoxy.

60. (Original) A compound or salt according to Claim 57, wherein:



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$R_{5B}$ and $R_{9B}$ are independently chosen from hydrogen, halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, amino, $C_{1-4}$alkyl, and $C_{1-2}$alkoxy.

61. (Original) A compound or salt according to Claim 57, wherein:

$R_{5B}$ represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, amino, $C_{1-4}$alkyl, and $C_{1-2}$alkoxy; and

$R_{9B}$ represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo($C_{1-2}$)alkyl, and $C_{1-2}$alkyl, and $C_{1-2}$alkoxy.

62. (Previously Amended) A compound or salt according to Claim 57, wherein:

$R_9$ is selected from the group consisting of halogen, cyano, $-N(SO_2CH_3)_2$, $-SO_2NH_2$, halo($C_{1-3}$)alkyl, and $C_{1-3}$alkoxy;

$R_{5B}$ represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, amino, $C_{1-4}$alkyl, and $C_{1-2}$alkoxy; and

$R_{9B}$ represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo($C_{1-2}$)alkyl, [and] $C_{1-2}$alkyl, and $C_{1-2}$alkoxy.



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63. (Previously Amended) A compound or salt according to Claim 57, wherein:

$R_5$ is selected from the group consisting of bromo, fluoro, iodo, halo($C_{1-6}$)alkyl, halo($C_{3-6}$)alkoxy, $C_{3-6}$alkyl substituted with 0-3 $R_6$, $C_{2-6}$alkenyl substituted with 0-3 $R_6$, Y, -(C=O)Y, -($CH_2$)Y, and -(CH(CN))Y;

$R_9$ is selected from the group consisting of halogen, cyano, -$N(SO_2CH_3)_2$, -$SO_2NH_2$, halo($C_{1-2}$)alkyl, $C_{1-3}$alkoxy;

$R_{5B}$ represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, amino, $C_{1-4}$alkyl, and $C_{1-2}$alkoxy; and

$R_{9B}$ represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo($C_{1-2}$)alkyl, $C_{1-2}$alkyl, and $C_{1-2}$alkoxy.

64. (Original) A compound or salt according to Claim 63, wherein:

$R_6$ is independently selected at each occurrence from the group consisting of cyano, halogen, hydroxy, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, -NH($C_{1-4}$alkyl), and -N($C_{1-4}$alkyl)( $C_{1-4}$alkyl) and Y; and

Y is independently selected at each occurrence from $C_{3-8}$ cycloalkyl, piperidinyl, piperazinyl,



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tetrahydropyranyl, dihydropyranyl, morpholinyl, thiomorpholinyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, and imidazolyl, each of which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo($C_{1-4}$)alkyl, halo($C_{1-4}$)alkoxy, mono- or di($C_{1-4}$)alkylamino, and $C_{1-4}$alkylthio.

65. (Original) A compound or salt according to Claim 63, wherein:

$R_9$ is cyano, trifluoromethyl, chloro, or iodo; and

$R_{9B}$ is hydrogen.

66. (Original) A compound according to Claim 50, which is N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

67. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-(4-cyclohexylphenyl)-2-



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methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

68. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl) phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

69. (Original) A compound according to Claim 50, which is (2R)-N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

70. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

71. (Original) A compound according to Claim 50, which is (2S)-4-(3-chloropyridin-2-yl)-N-(4-trifluoromethylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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72. (Original) A compound according to Claim 50, which is (2S)-N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

73. (Original) A compound according to Claim 50, which is (2S)-4-(3-chloropyridin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

74. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-(4-piperidin-1-ylphenyl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

75. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-[2-fluoro-4-(trifluoromethyl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

76. (Original) A compound according to Claim 50, which is (2R)-2-methyl-N-[4-(trifluoromethyl)phenyl]-4-[3-



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(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

77. (Original) A compound according to Claim 50, which is (2R)-N-(4-tert-butylphenyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

78. (Original) A compound according to Claim 50, which is (2R)-N-(4-isopropylphenyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

79. (Original) A compound according to Claim 50, which is 4-(3-chloropyridin-2-yl)-2,6-dimethyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

80. (Original) A compound according to Claim 50, which is N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2,6-dimethylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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81. (Original) A compound according to Claim 50, which is 4-(3-chloropyridin-2-yl)-N-(4-isopropylphenyl)-2,6-dimethylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

82. (Original) A compound according to Claim 50, which is (2R)-N-(4-cyclohexylphenyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

83. (Original) A compound according to Claim 50, which is 4-(3-chloropyridin-2-yl)-N-(4-cyclohexylphenyl)-2,6-dimethylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

84. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-(4-cyclopentylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

85. (Original) A compound according to Claim 50, which is (2R)-N-(4-cyclopentylphenyl)-2-methyl-4-[3-



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(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

86. (Cancelled)

87. (Cancelled)

88. (Original) A compound according to Claim 50, which is (2R)-N-(4-tert-butylphenyl)-4-(3-methoxypyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

89. (Original) A compound according to Claim 50, which is (2R)-4-(3-methoxypyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl] piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

90. (Original) A compound according to Claim 50, which is (2R)-N-(4-cyclohexylphenyl)-4-(3-methoxypyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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91. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-(3,6-dihydro-2H-pyran-4-yl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

92. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-(4-tetrahydro-2H-pyran-4-ylphenyl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

93. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

94. (Original) A compound according to Claim 50, which is (2R)-N-[4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl]-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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95. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[4-(2-methyl-1,3-thiazol-4-yl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

96. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-(2-ethyl-1,3-thiazol-4-yl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

97. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-(2-methoxy-1,1-dimethylethyl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

98. (Original) A compound according to Claim 50, which is (2R)-N-[4-(2-methoxy-1,1-dimethylethyl)phenyl]-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

99. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-(1-cyano-1-



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methylethyl)phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

100. (Original) A compound according to Claim 50, which is (2R)-N-[4-(1-cyano-1-methylethyl)phenyl]-2-methyl-4-[3-(trifluoromethyl) pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

101. (Original) A compound according to Claim 50, which is N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-ethylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

102. (Original) A compound according to Claim 50, which is 4-(3-chloropyridin-2-yl)-2-ethyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

103. (Original) A compound according to Claim 50, which is 4-(3-chloropyridin-2-yl)-2-ethyl-N-(4-isopropylphenyl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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104. (Original) A compound according to Claim 50, which is N-(4-tert-butylphenyl)-2-ethyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

105. (Original) A compound according to Claim 50, which is 2-ethyl-N-[4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

106. (Original) A compound according to Claim 50, which is 2-ethyl-N-(4-isopropylphenyl)-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

107. (Original) A compound according to Claim 50, which is 2-tert-butyl-N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

108. (Original) A compound according to Claim 50, which is 2-tert-butyl-N-[4-(trifluoromethyl)phenyl]-4-[3-



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(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

109. (Original) A compound according to Claim 50, which is N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-isopropylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

110. (Original) A compound according to Claim 50, which is N-(4-tert-butylphenyl)-2-isopropyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

111. (Original) A compound according to Claim 50, which is 2-isopropyl-N-[4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl) pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

112. (Original) A compound according to Claim 50, which is 2-isopropyl-N-(4-isopropylphenyl)-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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113. (Original) A compound according to Claim 50, which is (2R)-4-(3-fluoropyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

114. (Original) A compound according to Claim 50, which is (2R)-N-(4-tert-butylphenyl)-4-(3-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

115. (Original) A compound according to Claim 50, which is (2R)-4-(3-fluoropyridin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

116. (Original) A compound according to Claim 50, which is (2R)-N-(4-cyclohexylphenyl)-4-(3-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

117. (Original) A compound according to Claim 50, which is (2R)-N-(4-cyclopentylphenyl)-4-(3-fluoropyridin-2-



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yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

118. (Original) A compound according to Claim 50, which is (2R)-N-(4-tert-butylphenyl)-4-(3-cyanopyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

119. (Original) A compound according to Claim 50, which is (2R)-4-(3-cyanopyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

120. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-{4-[cyano(phenyl)methyl] phenyl}-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

121. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[3-methyl-4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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122. (Original) A compound according to Claim 50, which is (2R)-4-(3-fluoropyridin-2-yl)-2-methyl-N-[3-methyl-4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

123. (Original) A compound according to Claim 50, which is (2R)-4-{3-[bis(methylsulfonyl)amino]pyridin-2-yl}-N-(4-tert-butylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

124. (Original) A compound according to Claim 50, which is (2R)-2-methyl-N-[3-methyl-4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl] piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

125. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-{4-[1-(trifluoromethyl)vinyl]phenyl} piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

126. (Original) A compound according to Claim 50, which is (2R)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]-



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N-{4-[1-(trifluoromethyl)vinyl] phenyl}piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

127. (Original) A compound according to Claim 50, which is (2R)-4-(3-fluoropyridin-2-yl)-2-methyl-N-{4-[1-(trifluoromethyl)vinyl] phenyl}piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

128. (Original) A compound according to Claim 50, which is (2R)-N-(4-sec-butylphenyl)-4-(3-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

129. (Original) A compound according to Claim 50, which is (2R)-2-methyl-N-[4-(2,2,2-trifluoro-1-methylethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

130. (Original) A compound according to Claim 50, which is (2R)-4-(3-fluoropyridin-2-yl)-2-methyl-N-[4-(2,2,2-trifluoro-1-methylethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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131. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloro-5-nitropyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

132. (Original) A compound according to Claim 50, which is (2R)-4-(5-amino-3-chloropyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

133. (Original) A compound according to Claim 50, which is (2R)-4-(3-fluoropyridin-2-yl)-N-[3-fluoro-4-(trifluoromethyl) phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

134. (Original) A compound according to Claim 50, which is (2R)-N-[3-fluoro-4-(trifluoromethyl)phenyl]-2-methyl-4-[3-(trifluoromethyl) pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

135. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[4-



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(2,2,2-trifluoro-1-methylethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

136. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-(2,2,4,4-tetrafluoro-4H-1,3-benzodioxin-6-yl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

137. (Original) A compound according to Claim 50, which is (2R)-4-(3-fluoropyridin-2-yl)-2-methyl-N-(2,2,4,4-tetrafluoro-4H-1,3-benzodioxin-6-yl)piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

138. (Original) A compound according to Claim 50, which is (2R)-2-methyl-N-(2,2,4,4-tetrafluoro-4H-1,3-benzodioxin-6-yl)-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

139. (Original) A compound according to Claim 50, which is (2R)-4-[3-(aminosulfonyl)pyridin-2-yl]-N-(4-tert-butylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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140. (Original) A compound according to Claim 50, which is (2R)-N-(4-benzoylphenyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

141. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-(4-iodophenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

142. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-{4-[2,2,2-trifluoro-1,1-bis(trifluoromethyl)ethyl]phenyl}piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

143. (Original) A compound according to Claim 50, which is (2R)-2-methyl-N-{4-[2,2,2-trifluoro-1,1-bis(trifluoromethyl)ethyl] phenyl}-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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144. (Original) A compound according to Claim 50, which is (2R)-N-(4-butylphenyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

145. (Original) A compound according to Claim 50, which is 2-(fluoromethyl)-N-[4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

146. (Original) A compound according to Claim 50, which is (2R)-N-[4-bromo-3-(trifluoromethyl)phenyl]-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

147. (Original) A compound according to Claim 50, which is (2R)-N-[4-bromo-3-(trifluoromethyl)phenyl]-2-methyl-4-[3-(trifluoromethyl) pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

148. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-N-[4-fluoro-3-



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(trifluoromethyl) phenyl]-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

149. (Original) A compound according to Claim 50, which is (2R)-N-[4-fluoro-3-(trifluoromethyl) phenyl]-2-methyl-4-[3-(trifluoromethyl) pyridin-2-yl] piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

150. (Original) A compound according to Claim 50, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl] phenyl}piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

151. (Original) A compound according to Claim 50, which is (2R)-2-methyl-N-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl) ethyl]phenyl}-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

152. (Original) A compound according to Claim 40, which is (2R)-N-(4-tert-butylphenyl)-4-(3-chloropyrazin-2-



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yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

153. (Original) A compound according to Claim 40, which is (2R)-4-(3-chloropyrazin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

154. (Original) A compound according to Claim 40, which is (2R)-4-(3-chloropyrazin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

155. (Original) A compound according to Claim 40, which is (2R)-4-(3-chloropyrazin-2-yl)-2-methyl-N-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl] phenyl} piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

156. (Original) A compound according to Claim 40, which is (2R)-4-(3-chloropyrazin-2-yl)-2-methyl-N-{4-cyclopentyl-phenyl} piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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157. (Original) A compound according to Claim 40, which is (2R)-4-(3-chloropyrazin-2-yl)-2-methyl-N-{4-cyclohexyl-phenyl} piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

158. (Original) A compound according to Claim 42, which is 4-(3-chloropyridin-2-yl)-N-[5-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

159. (Original) A compound according to Claim 42, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[5-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

160. (Original) A compound according to Claim 42, which is (2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[6-(trifluoromethyl)pyridin-3-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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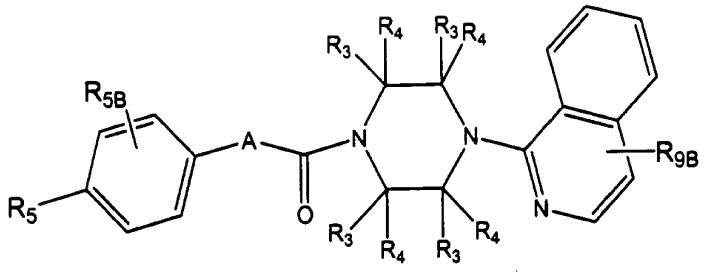
161. (Previously Amended) A compound of the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, $NR_A$, $CR_BR_B'$, $NR_ACR_BR_B'$, $CR_B\ R_B'NR_A$, $-CR_A=CR_B-$, and $C_3H_4$; where $R_A$, $R_B$, and $R_B'$ are independently selected at each occurrence from hydrogen [or] and $C_{1-6}$ alkyl;

$R_3$ and $R_4$ are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, -NH($C_{1-6}$alkyl), and -N($C_{1-6}$alkyl)($C_{1-6}$alkyl);

$R_5$ is selected from the group consisting of halogen, halo($C_{1-6}$)alkyl, $C_{3-6}$alkyl substituted with 0-3 $R_6$, $C_{2-6}$alkenyl substituted with 0-3 $R_6$, ($C_{3-8}$cycloalkyl)$C_{1-4}$alkyl substituted with 0-3 $R_6$, and Y;

$R_{5B}$ and $R_{9B}$ each represent from 0 to 2 substituents and are independently chosen from halogen, cyano, nitro,



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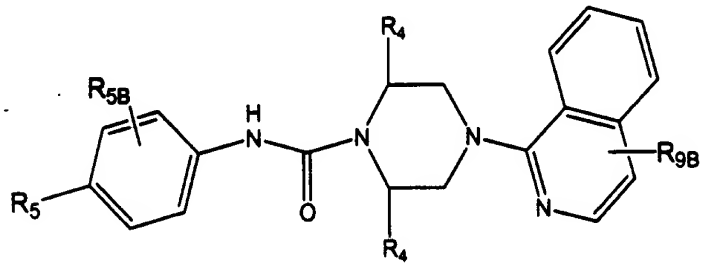
halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, amino, $C_{1-4}$alkyl, and $C_{1-2}$alkoxy;

$R_6$ is independently selected at each occurrence from the group consisting of cyano, halogen, hydroxy, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, -NH($C_{1-4}$alkyl), -N($C_{1-4}$alkyl)($C_{1-4}$alkyl) and Y;

Y is independently selected at each occurrence from $C_{3-8}$ cycloalkyl, piperidinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, morpholinyl, thiomorpholinyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, and imidazolyl, each of which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, halo($C_{1-4}$)alkyl, halo($C_{1-4}$)alkoxy, mono- or di($C_{1-4}$)alkylamino, and $C_{1-4}$alkylthio.

162. (Original) A compound or salt according to Claim 161 of the Formula:




wherein



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$R_4$ is independently selected at each occurrence from hydrogen and $C_{1-4}$alkyl.

163. (Original) A compound or salt according to Claim 162, wherein:

$R_5$ is selected from the group consisting of halo($C_{1-6}$)alkyl, $C_{3-6}$alkyl, ($C_{3-8}$cycloalkyl)$C_{1-4}$alkyl, and Y;

$R_{5B}$ and $R_{9B}$ each represent from 0 to 1 substituents and are independently chosen from halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, amino, $C_{1-4}$alkyl, and $C_{1-2}$alkoxy;

Y is selected from $C_{3-8}$ cycloalkyl, piperidinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, morpholinyl, thiomorpholinyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, and imidazolyl.

164. (Original) A compound according to Claim 161, which is(2R)-4-isoquinolin-1-yl-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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165. (Original) A compound according to Claim 161, which is (2R)-N-(4-tert-butylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

166. (Original) A compound according to Claim 161, which is (2R)-N-(4-isopropylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

167. (Original) A compound according to Claim 161, which is (2R)-N-(4-cyclopentylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

168. (Original) A compound according to Claim 161, which is (2R)-N-(4-cyclohexylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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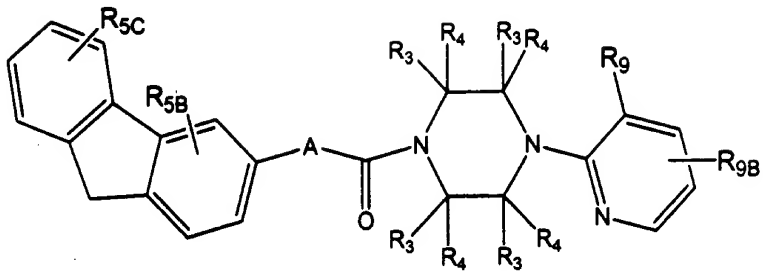
169. (Previously Amended) A compound of the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, $NR_A$, $CR_BR_B'$, $NR_ACR_BR_B'$, $CR_BR_B'NR_A$, $-CR_A=CR_B-$, and $C_3H_4$; where $R_A$, $R_B$, and $R_B'$ are independently selected at each occurrence from hydrogen and $C_{1-6}$ alkyl;

$R_3$ and $R_4$ are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo($C_{1-6}$)alkyl, halo($C_{1-6}$)alkoxy, hydroxy, amino, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $-NH(C_{1-6}alkyl)$, and $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$;

$R_{5B}$, $R_{5C}$, and $R_{9B}$ each represent from 0 to 2 substituents and are independently chosen from halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, amino, $C_{1-4}$alkyl, and $C_{1-2}$alkoxy; and

$R_9$ is selected from the group consisting of halogen, cyano, $-N(SO_2CH_3)_2$, $-SO_2NH_2$, halo($C_{1-3}$)alkyl, $C_{1-3}$alkoxy, $-NH(C_{1-3}alkyl)$, and $-N(C_{1-3}alkyl)(C_{1-3}alkyl)$.



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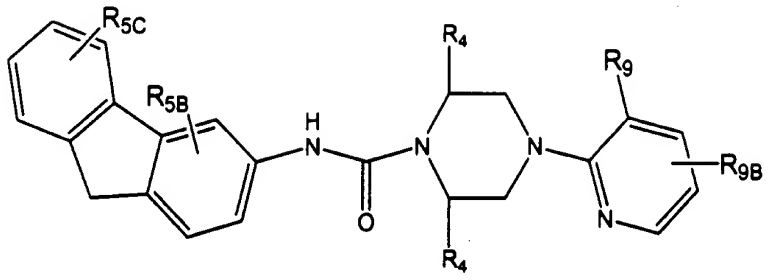
170. (Original) A compound or salt according to Claim 169 of the Formula:




wherein

$R_4$ is independently selected at each occurrence from hydrogen and $C_{1-4}$alkyl.

171. (Original) A compound or salt according to Claim 170, wherein:

$R_9$ is selected from the group consisting of halogen and halo($C_{1-2}$)alkyl; and

$R_{5B}$ and $R_{9B}$ each represent from 0 to 1 substituents and are independently chosen from halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, amino, $C_{1-4}$alkyl, and $C_{1-2}$alkoxy.

172. (Original) A compound according to Claim 169, which is(2R)-4-(3-chloropyridin-2-yl)-N-(9H-fluoren-2-yl)-



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2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

173. (Original) A compound according to Claim 169, which is (2R)-N-(9H-fluoren-2-yl)-2-methyl-4-[3-(trifluoromethyl) pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

174. (Original) A compound according to Claim 38, which is (2R)-N-(4-tert-butylcyclohexyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

175. (Original) A compound according to Claim 38, which is (2R)-4-(3-chloropyridin-2-yl)-N-(4-isopropylcyclohexyl)-2-methylpiperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.

176. (Original) A compound according to Claim 38, which is (2R)-N-(4-isopropylcyclohexyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide, or a pharmaceutically acceptable salt thereof.



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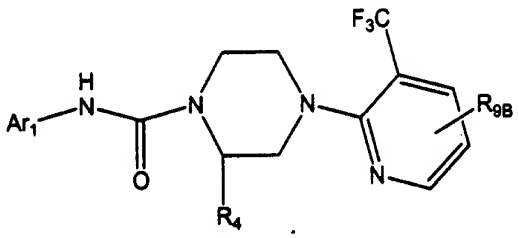
177-192. (Cancelled)

193. (Original) A compound or salt of Claim 50 wherein the compound or salt is not addictive.

194-196. (Cancelled)

197. (Original) A compound of the Formula




or a pharmaceutically acceptable salt thereof wherein:

$R_4$ is methyl or hydrogen;

$R_{9B}$ represents 0-2 substituents independently chosen from: halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, amino, $C_{1-4}$alkyl, and $C_{1-2}$alkoxy; and

$Ar_1$ is 2,4-dichlorphenyl or 3-nitro-4-chlorophenyl.

198. (Original) A compound of the Formula



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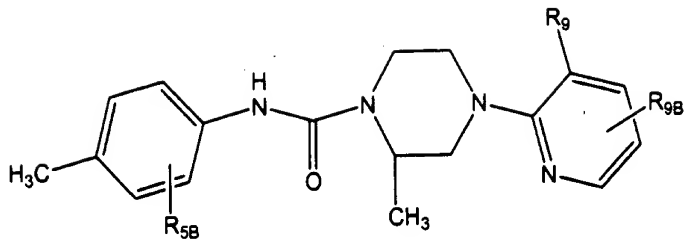

or a pharmaceutically acceptable salt thereof wherein:

$R_9$ is chloro or trifluoromethyl; and

$R_{5B}$ and $R_{9B}$ independently represent from 0-2 substituents on each of the rings on which they occur and are independently chosen from: halogen, cyano, nitro, halo($C_{1-2}$)alkyl, halo($C_{1-2}$)alkoxy, amino, $C_{1-4}$alkyl, and $C_{1-2}$alkoxy.

199. (Previously added) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound or salt according to claim 4.

200. (Previously added) A package comprising a pharmaceutical composition of claim 199 in a container and further comprising indicia comprising instructions for using the composition to alleviate pain.



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201. (Previously added) A package comprising a pharmaceutical composition of claim 199 in a container and further comprising indicia comprising instructions for using the composition to alleviate symptoms of exposure to capsaicin or tear gas.

202. (Previously added) A compound or salt of claim 4 wherein, in an *in vitro* assay of capsaicin receptor antagonism, the compound or salt exhibits capsaicin receptor antagonist activity, but in an in vitro assay of capsaicin receptor agonism the compound does not exhibit detectable agonist activity.

203. (Previously added) A compound or salt of claim 4 wherein a dose of the compound or salt that is twice the minimum dose sufficient to provide analgesia in an animal model for determining pain relief does not produce sedation in an animal model assay of sedation.

204. (Previously added) 4-(3-Chloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide or a pharmaceutically acceptable salt thereof.



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205. (Previously added) (2R)-N-(4-tert-butylphenyl)-4-[3-(dimethylamino)pyridin-2-yl]-2-methylpiperazine-1-carboxamide or a pharmaceutically acceptable salt thereof.

206. (Previously added) (2R)-4-[3-(dimethylamino)pyridin-2-yl]-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide or a pharmaceutically acceptable salt thereof.

207. (Previously added) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound or salt according to claim 27.

208. (Previously added) A compound or salt of claim 27 wherein, in an *in vitro* assay of capsaicin receptor antagonism, the compound or salt exhibits capsaicin receptor antagonist activity, but in an in vitro assay of capsaicin receptor agonism the compound does not exhibit detectable agonist activity.

209. (Previously added) A compound or salt of claim 27 wherein a dose of the compound or salt that is twice the minimum dose sufficient to provide analgesia in an animal



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model for determining pain relief does not produce sedation in an animal model assay of sedation.

210. (Previously added) A package comprising a pharmaceutical composition of claim 207 in a container and further comprising indicia comprising instructions for using the composition to alleviate pain.

211. (Previously added) A package comprising a pharmaceutical composition of claim 207 in a container and further comprising indicia comprising instructions for using the composition to alleviate symptoms of exposure to capsaicin or tear gas.



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